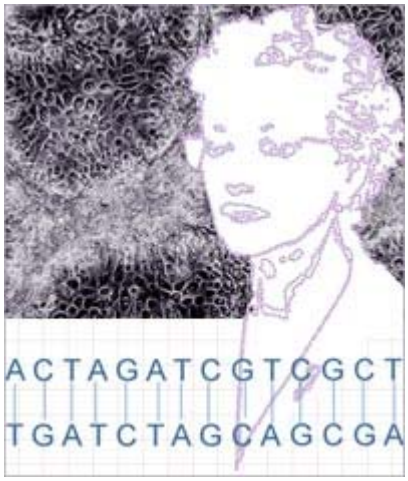
Training

Fact Sheet on Genetic Testing for Breast and Ovarian Cancer Susceptibility



Introduction

Genetic testing for hereditary susceptibility for breast and ovarian cancer is the first genetic test to be marketed directly to consumers. Public health agencies may be called upon to answer questions about this testing from the general public and healthcare providers in their communities. This fact sheet contains information about the genetic test for hereditary susceptibility for breast and ovarian cancer, the clinical context in which it is currently used, and some of the potential ethical and social issues.

The burden of breast and ovarian cancer in the United States

One in eight (12%) of U.S. women aged 90 years or younger will develop breast cancer sometime during her lifetime (1). One in 70 (1.4%) will develop ovarian cancer (2).

About 200,000 U.S. women and 1500 men develop breast cancer each year (3).

About 23,000 U.S. women develop ovarian cancer each year (3).

Female sex, increasing age, and family history of breast and/or ovarian cancer are the three greatest risk factors for both breast cancer and ovarian cancer (2).

What are BRCA-1 and BRCA-2?

BRCA-1 stands for breast cancer gene number one because it was the first breast/ovarian cancer-related gene discovered. BRCA-2 was the second breast/ovarian cancer-related gene discovered. Some changes (mutations) in these genes increase the risk for breast and ovarian cancer.

Inherited mutations in genes other than BRCA-1 and BRCA-2 have been shown or are suspected to increase susceptibility for developing breast and other forms of cancer. Testing is available for some of these mutations. Mutations in these genes (such as TP53 and PTEN) are much less common than mutations in BRCA-1 or BRCA-2 (2).

The genetics of hereditary breast cancer susceptibility due to BRCA-1 or BRCA-2

About 5%-10% of women in whom breast or ovarian cancer is diagnosed have a hereditary form of cancer due to mutations in the BRCA-1 or BRCA-2 genes (2).

BRCA-1 and BRCA-2 mutations can be inherited from either the mother or the father.

Testing is available that will determine if there are mutations in the BRCA-1 or the BRCA-2 genes (4).

A genetic counselor or physician who specializes in genetics or oncology can provide the most complete information about genetic testing for BRCA mutations and the most complete answers about the options for cancer prevention and early detection.

Prevalence of BRCA-1 and BRCA-2 mutations

About 1 in 800 persons in the general population carry a mutation in BRCA-1 that may result in an increased risk for breast and/or ovarian cancer (2, 5).

The prevalence in the general population of BRCA-2 mutations associated with an increased risk of cancer is unknown (10).

About 1 in 40 (2.5%) of Ashkenazi Jewish descent carry one of three common mutations that may result in an increased risk for breast and/or ovarian cancer. Two of these mutations are in BRCA-1 (del185AG and 5382insC) and one mutation is in BRCA-2 (6174delT)(6).

Who is most likely to have a BRCA-1 or BRCA-2 mutation?

Most women do not have a mutation in the BRCA-1 or BRCA-2 gene. The National Cancer Institute has stated (2) that some factors, that may be independent of each other, increase the likelihood that a person carries an inherited BRCA mutation. They include:

1. A family history of several (three or more) close blood relatives (sisters, daughters, mother, grandmothers, aunts) affected with breast cancer, ovarian cancer, or both.
2. A family history of early onset (before 50 or before menopause) breast or ovarian cancer in one or more close blood relatives (sisters, daughters, mother, grandmothers, or aunts).
3. A family history of one or more close blood relatives (sisters, daughters, mother, grandmothers, aunts) with two or more primary tumors of the breast or bilateral breast cancer.
4. A family history of one or more close male blood relatives (father, sons, brothers, uncles, grandfathers) who have developed breast cancer.
5. Ashkenazi (Eastern European) Jewish ancestry and a family history of breast and/or ovarian cancer.

However, even when one or more of these identified risk factors are present, most women will not have a mutation in BRCA 1 or BRCA 2 (7). Overall, the likelihood of detecting a mutation in BRCA1/2 in relation to these risk factors is about 17% (7).

Remember, both maternal and paternal family history is relevant for determining a person's risk for breast/ovarian cancer. Women who meet one or more of the above criteria can contact their primary health providers for referral for genetic counseling and cancer risk assessment to discuss their risks for breast and/or ovarian cancer and whether BRCA testing is clinically appropriate for their situation.

Eligibility for BRCA-1 and BRCA-2 testing

Guidelines for assessment, counseling and testing for genetic susceptibility for breast and ovarian cancer have been developed by the American College of Medical Genetics and the New York Department of Health (11) The CDC has not established testing guidelines. These guidelines describe the process for assessing cancer risk(11). Most often, the first person that is tested in a family for BRCA-1 and BRCA-2 mutations is one who developed breast or ovarian cancer since this determines if the cancer in the family is associated with a BRCA mutation. If a mutation is found, it becomes a simple matter to test other blood relatives for the same mutation. If a mutation is not found in the family

member who has or had cancer, the test is not informative and would not provide helpful information to other family members. If no family members with cancer are living or available for testing, testing options are generally considered on a case-by-case basis for each family.

Interpreting a positive BRCA-1 or BRCA-2 test result: the basics

A positive result means that a mutation in BRCA-1 or BRCA-2 has been detected.

Mutations in BRCA-1 or BRCA-2 are associated with lifetime risks for breast cancer of 36% - 85% and with lifetime risk for ovarian cancer of 16% - 60%, depending on the population studied (2). Many women who have a mutation in BRCA-1 or BRCA-2 will not develop breast cancer.

The highest published risk (85%) for breast and/or ovarian cancer associated with BRCA-1 or BRCA-2 mutations has been found in studies of families that have three or more blood relatives affected with breast and/or ovarian cancer (6).

The lowest published risk (36%) for breast cancer associated with BRCA-1 or BRCA-2 mutations was reported from a study of Ashkenazi Jewish women with breast cancer who were tested for two mutations in BRCA-1 (185delAG and 5382insC) and one mutation in BRCA-2 (6174delT) (8).

The lowest published risk (15%) for ovarian cancer associated with BRCA-1 or BRCA-2 mutations was reported from a population-based study of 5000 well Ashkenazi Jewish women and their family members (9).

Mutations in BRCA-1 and BRCA-2 also have been associated with an increased risk of male breast cancer (especially BRCA-2 mutations) and prostate cancer. Some evidence suggests that other cancers also may be increased in mutation carriers.

Interpreting a negative BRCA-1 or BRCA-2 test result: the basics

A negative test result means that no mutation was detected in the BRCA-1 or BRCA-2 gene. The meaning of a negative test result depends on whether a mutation in BRCA-1 or BRCA-2 was identified in a family member with cancer.

For families in which a BRCA-1 or BRCA-2 mutation has been documented, a negative test result for an unaffected blood relative means that the lifetime risk of breast cancer is the same as women without a family history of breast cancer (one in eight).

For women from families in which a BRCA-1 or BRCA-2 mutation has not been documented in a blood relative, a negative test result probably will not provide helpful information for assessing the risk of cancer for a member of that family. In other words, the test will be uninformative. In this situation, cancer risk will be estimated on the basis of family and medical history and environmental and lifestyle factors. (9)

Test results of uncertain clinical significance

Sometimes BRCA-1 or BRCA-2 test results reveal mutations of unknown significance. Information about these mutations is insufficient to determine whether they are associated with an increased risk for breast cancer or are normal variations (polymorphisms). One study reported finding variants of unknown significance in 13% of patients tested (7).

Clinical utility of BRCA-1 and BRCA-2 test results: the basics

The risks associated with mutations in BRCA-1 and BRCA-2 mutations cannot be quantified precisely. Information is limited on how other non-genetic factors influence the risks associated with these mutations.

However, results from BRCA genetic testing may be useful as an additional piece of information in determining appropriate clinical management strategies for prevention and early detection of breast and ovarian cancers in high-risk women, according to the American College of Medical Genetics (9, 11).

For people who have a BRCA mutation, clinical management choices may include increased or more intensive monitoring, chemoprevention, or prophylactic surgery to remove at-risk organs. Although some of these options may reduce the risk for developing breast and/or ovarian cancer, no option totally eliminates this risk (2).

Ethical, legal, and social implications associated with BRCA-1 and BRCA-2 testing

Any woman who seeks this testing must be well informed about the risks and benefits of the testing. This is best accomplished through a genetic risk evaluation that includes informed consent and genetic counseling, according to the American College of Medical Genetics (11).

A positive BRCA genetic test result in one person may mean that an entire at-risk family has been identified. Issues related to communicating with other family members who may or may not wish to have this information need to be considered when making a testing decision.

Receiving BRCA test results, either positive or negative, may affect emotional health and self esteem. People should consider the possible emotional reactions before being tested.

Genetic test results that uncover a genetic susceptibility for breast and/or ovarian cancer may put the tested person at risk for discrimination by health insurance providers, employers, and others according the American College of Medical Genetics (11). Although genetic discrimination related to cancer susceptibility testing has not been commonly observed, it should be considered as a possibility when making a testing decision.

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